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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 91/09593
A61K 31/00	A2	(43) International Publication Date:	11 July 1991 (11.07.91)

(21) International Application Number: PCT/GB90/01996

(22) International Filing Date: 20 December 1990 (20.12.90)

(30) Priority data:
8928837.7 21 December 1989 (21.12.89) GB

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: 5-HT_3 ANTAGONISTS FOR TREATMENT OF NAUSEA, BRADYCARDIA OF HYPOTENSION ASSOCIATED WITH MYOCARDIAL INSTABILITY

(57) Abstract

A method for the treatment and/or prophylaxis of nausea and bradycardia and/or hypotension associated with myocardial instability in mammals, such as humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis an effective and/or prophylactic amount of a 5-HT_3 receptor antagonist, such as a compound of formula (I): X-A-R, or a pharmaceutically acceptable salt thereof, wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; and R is a saturated azabicyclic moiety or an imidazolyl moiety.

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5-HT_3 ANTAGONISTS FOR TREATMENT OF NAUSEA, BRADYCARDIA OF HYPOTENSION ASSOCIATED WITH MYOCARDIAL INSTABILITY

The present invention relates to a method for the treatment and/or prophylaxis of nausea and bradycardia associated with myocardial instability.

EP-A-158265, EP-A-200444, EP-A-220011, EP-A-215545, EP-A-247266, EP-A-230718, EP-A-235878, EP-A-254584, EP-A-255297, EP-A-261964, EP-A-287196, EP-A-289170, EP-A-315390 and EP-A-377967 (Beecham Group p.l.c.), EP-A-158532 and EP-A-237281 (A.H. Robins Company, Inc.), EP-A-67770 and EP-A-2666730 (Merrell Toraude et Compagnie), GB 2125398A, GB 2145416A and 2152049A (Sandoz Limited), EP-A-322016, 350129 and 350130 (Duphar international Research B.V.), EP-A-307172 and US 4921982 (Eli Lilly and Company), EP-A-323077, EP-A-306148 and GB 2208385A and EP-A-361629 (John Wyeth and Brother Limited), EP-A-234872 (Adria Laboratories Inc.), EP-A-294292 (Adir et Compagnie), EP-A-339950, US 4924010, 4920219, 4290227 and WO90/6309 (Rorer International (overseas), Inc.), EP-A-309423 and EP-A-351385 (Instituto de Angeli S.p.A.), EP-A-313393 (Yoshitomi Pharmaceutical industries Limited) EP-A-378111 (Zambon), EP-A-376624 and EP-A-381422 (Yamanouchi), EP-A-328200 and EP-A-337547 (Merck, Sharp and Dohme Limited), EP-A-302699 (Fordonal), WO 90/14347 (Nippon Skinyaku Co. Limited) and EP-A-358903 (Dianippon Pharmaceutical Co. Ltd.) disclose classes of compounds containing a saturated azacyclic or azabicyclic moiety, such as tropanyl, granatyl or quinuclidinyl, and are 5-HT_3 receptor antagonists.

GB 2153821A, EP-A-191562, EP-A-210840, EP-A-219193, EP-A-242973, EP-A-276163, EP-A-291172, EP-A-307145, EP-A-317088, EP-A-336759, EP-A-339959, EP-A-344015, EP-A-345956, EP-A-347229, EP-A-353983, EP-A-356098, EP-A-357414, EP-A-357415, EP-A-357416, EP-A-357417,

EP-A-364274 and EP-A-385722 (Glaxo Group Limited), EP-A-315316 (Beecham Group p.l.c.), EP-A-361317 (Fujisawa), EP-A-375045 and EP-A-377238 (Duphar), EP-A-376624 and EP-A-381422 (Yamanouchi Pharmaceutical Co. Ltd.), EP-A-392663 (Ono Pharmaceutical Co. Limited), EP-A-373061 (Adir et Compagnie), US 4914207 (Pfizer) and GB 2229182A (Merck Sharp and Dohme Limited) describe further classes of compounds which also have 5-HT_3 receptor antagonist activity, and containing an unsaturated N-heterocycle, such as an imidazolyl moiety.

EP-A-201165 (Beecham Group p.l.c.) discloses the use of 5-HT_3 receptor antagonists, in particular MDL 72222 (Example 1), ICS 205-930 (Example 2) and ondansetron (Example 5) as antiemetic agents. EP-A-200444 (Example 6) discloses the 5-HT_3 receptor antagonist, granisetron, which is also disclosed as an antiemetic agent. Ondansetron and granisetron are under clinical evaluation as antiemetic agents in cytotoxic drug induced emesis.

Myocardial instability occurs as a result of myocardial infarction, myocardial reperfusion following thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), coronary bypass grafts and coronary cardiac catheterisation. Nausea, bradycardia (slowing of the heart) and hypotension as a result of myocardial instability is well known (E. Braunwald, Heart Disease' publ. Saunders pp. 1197-8, 1236, 1253, 1264), and there is a need for a suitable treatment to overcome these problems.

It has now been discovered that 5-HT_3 receptor antagonists, such as compounds of the above classes, are of potential use in the treatment or prophylaxis of nausea, bradycardia and/or hypotension associated with myocardial instability.

Accordingly, the present invention provides a method for the treatment and/or prophylaxis of nausea and bradycardia

and/or hypotension associated with myocardial instability in mammals, such as humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis an effective and/or prophylactic amount of a 5-HT_3 receptor antagonist, such as a compound of formula (I), or a pharmaceutically acceptable salt thereof:

X-A-R (I)

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety; and

R is a saturated azabicyclic moiety or an imidazolyl moiety.

X may be unsubstituted or substituted, usually by one or more substituents selected from halogen, C_{1-6} alkoxy, C1-6 alkylthio, C_{1-6} alkyl, hydroxy, amino, C_{1-6} alkylamino, C_{1-7} alkanoylamino, or two substituents on X (when fused), may be linked to form a saturated or unsaturated optionally substituted carbocyclic ring.

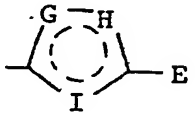
Heteroatoms for heteroaryl and heterocyclic groups are selected from oxygen, nitrogen and sulphur.

X may be joined to A by an aromatic carbon atom, or (when X is fused), by a carbocyclic ring carbon atom, or by a heterocyclic ring carbon or nitrogen atom. When X is fused, and A is attached at an aromatic carbon atom, it is preferably attached at the aromatic carbon adjacent a 'fused' carbon atom, which is attached to the heteroatom of a heterocyclic ring in formula (I).

X may also be further joined to A as defined hereinafter, when Y-R_{10} is N-B=N.

Suitable examples of X are as described in the aforementioned patent publications relating to 5-HT_3 receptor antagonists containing a saturated azabicyclic moiety, the subject matter of which is incorporated herein by reference.

Suitable examples of A include CONH (amide), COO (ester), NHCONH (ureide), CONHCONH (extended ureide), or a group of structure (h):



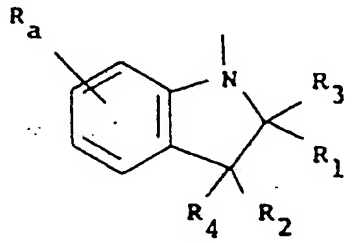
(h)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy.

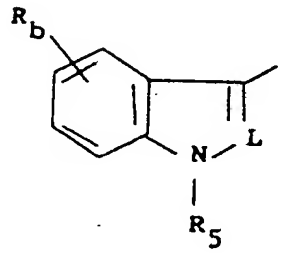
A may also be a keto - (methylene or ethylene) linkage, such as -CO-$(CH_2)_2$-, or another of the linkages as described in the abovementioned patent publications relating to further classes of compounds having 5-HT_3 receptor antagonist activity containing an unsaturated N-heterocycle, in particular those in the name of Glaxo Group Limited.

For the avoidance of doubt, the suitable X values in formula (I) which are described in the referenced patent publications, are that part of the structure remaining when the saturated azabicyclic moiety and A (where A is one of the suitable examples listed above), are disregarded.

Preferred examples of X include a group of sub-formula (a), (b), (c), (d), (e), (f) or (g):



(a)



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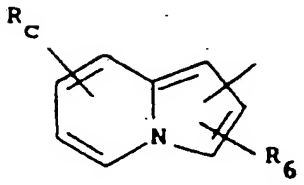

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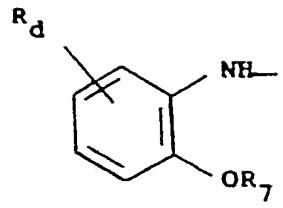

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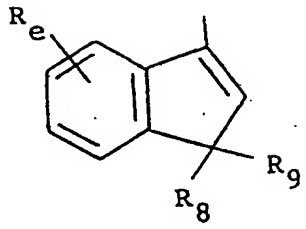
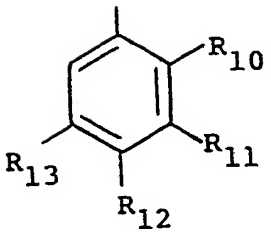
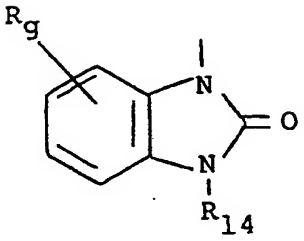


(e)



(f)



(g)

wherein

R_a to R_e and R_g are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or
R_1 and R_2 together are a bond;
R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and
R_4 together with R_2 may be C_{2-7} polymethylene when R_1 is hydrogen;
R_8 and R_9 are independently selected from hydrogen or C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;
either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and
R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or
R_{10} and R_{11} are joined to form $-OCH(R_uR_v)-E-$ wherein E is $(CH_2)_n$ or $NR_wCO(CH_2)m$ wherein n is 1 or 2 and m is 0 or 1 and R_u, R_v and R_w are independently selected from hydrogen or C_{1-6} alkyl;
R_{12} is hydrogen, C_{1-6} alkoxy or amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and
R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;
R_{14} is hydrogen or C_{1-6} alkyl; and
L is CH or N.

Examples of moieties in alkyl or alkyl containing groups in R_1 to R_{14} include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably methyl.

Suitable examples of R_2 and R_4 or R_8 and R_9 when joined include C_2, C_3, C_4, C_5 or C_6 polymethylene, preferably C_2, C_3, C_4 or C_5 polymethylene.

R_a to R_e and R_g are preferably selected from hydrogen, fluoro, chloro and hydroxy, most preferably hydrogen. R_b may be 5-, 6- or 7-chloro or fluoro.

When X is of sub-formula (a), one of R_1 and R_3 is preferably hydrogen and one or both of R_2 and R_4 (most preferably both) are alkyl groups, such as methyl, or are joined to form C_{2-7} polymethylene; or when one of R_2 and R_4 is hydrogen, the other is preferably ethyl or n- or iso- propyl.

When X is of sub-formula (b), R_5 is preferably hydrogen or a methyl or ethyl group.

When X is of sub-formula (c), one of A and R_6 is attached at the 1-position and the other is attached at the 3-position as depicted in sub-formula (c), and R_6 is preferably methyl or ethyl.

When X is of sub-formula (d), R_7 is preferably methyl.

When X is of sub-formula (e), R_8 and R_9 are preferably both methyl groups.

When X is of sub-formula (f), and R_{10} is C_{1-6} alkoxy or is joined to Y, R_{12} is preferably amino and R_{13} is preferably chloro or bromo, most preferably chloro. R_{10} is preferably methoxy when C_{1-6} alkoxy.

When X is of sub-formula (f), and R_{10} is hydrogen, R_9 and R_{11} are preferably chloro or methyl and R_{10} is preferably hydrogen.

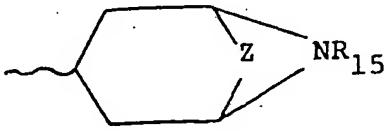
When X is of sub-formula (g), R_{14} is preferably hydrogen or methyl.

X is preferably a group of sub-formula (e).

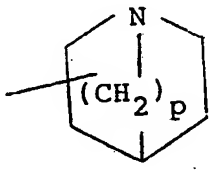
Suitable examples of R are as described in the aforementioned patent publications relating to 5-HT_3

receptor antagonists containing a saturated azabicyclic moiety.

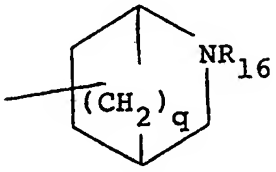
Preferred examples of R then include the groups of sub-formula (i), (j) and (k):



(i)



(j)



(k)

wherein

Z is $(CH_2)_n$ wherein n is 2 or 3, or Z is CH_2-O-CH_2;
p and q are independently 1 to 3; and
R_{15} or R_{16} is methyl or ethyl, preferably methyl.

R is most preferably endo-9-azabicyclo[3.2.1]non-3-yl, endo-8-azabicyclo[3.2.1]oct-3-yl, 9-aza-3-oxabicyclo-[3.2.1]non-7-yl or 3-quinuclidinyl. R may also be an

imidazolyl group, in particular, 5-methyl-4-imidazolyl.

Examples of the compounds of formula (I) include the examples described in the aforementioned Patent Publications/References disclosing compounds containing a saturated azabicyclic moiety. Particular examples include MDL 72222, ICS 205-930 (tropisetron) and PU 46470A, described in Example 5 of EP-A-247266, and granisetron.

Examples of compounds of formula (I) also include the examples described in the aforementioned Patent Publications/References disclosing compounds containing an imidazolyl moiety, in particular, ondansetron and Examples 1, 2, 3, 4 and 5 in EP-A-315316 (Beecham Group p.l.c.).

Examples of pharmaceutically acceptable salts are as described in the aforementioned European Patent references in the name of Beecham Group p.l.c., the subject matter of which is incorporated herein by reference.

Further 5-HT_3 receptor antagonists are as described and claimed in the aforementioned patent publications, in particular, those in the name of Glaxo Group Limited.

References to a 5-HT_3 receptor antagonist, including compounds of formula (I) and the specific compounds mentioned hereinbefore and salts thereof, include solvates such as hydrates.

5-HT_3 receptor antagonists may be identified by standard methods, such as tests involving antagonism of the von Bezold Jarisch reflex, as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980).

The compounds of formula (I), including the specific compounds mentioned hereinbefore and salts thereof may be prepared as described in the aforementioned Patent Publications/References.

Preferably, the 5-HT_3 receptor antagonist is in substantially pure pharmaceutically acceptable form.

The administration of the 5-HT_3 receptor antagonist may be by way of oral, sublingual, transdermal or parenteral administration.

Parenteral administration will generally be preferred, and the 5-HT_3 receptor antagonist administered during or after cardiac treatment (thrombolysis, PTCA, coronary bypass grafts, coronary and cardiac catheterisation). In the case of prophylaxis, however, the preferred administration may be pretreatment by way of oral, sublingual or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the 5-HT_3 receptor antagonist, such as a compound of formula (I) or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.1 to 5 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

For oral or parenteral administration, it is greatly preferred that the 5-HT_3 receptor antagonist is administered

in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for

reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the 5-HT_3 receptor antagonist and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is

included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

The present invention also provides the use of a 5-HT_3 receptor antagonist, such as a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment and/or prophylaxis of nausea, bradycardia and/or hypotension associated with myocardial instability. Such treatment and/or prophylaxis may be carried out as hereinbefore described.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of nausea, bradycardia and/or hypotension associated with myocardial instability, which comprises a 5-HT_3 receptor antagonist, such as a compound of formula (I) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

Claims

1. A method for the treatment and/or prophylaxis of nausea and bradycardia and/or hypotension associated with myocardial instability in mammals, such as humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis an effective and/or prophylactic amount of a 5-HT_3 receptor antagonist.

2. Use of a 5-HT_3 receptor antagonist in the treatment and/or prophylaxis of nausea, bradycardia and/or hypotension associated with myocardial instability.

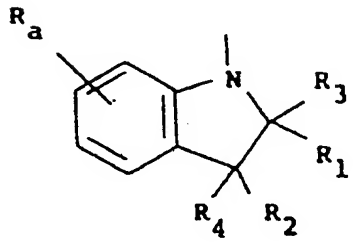
3. A pharmaceutical composition for use in the treatment and/or prophylaxis of nausea, bradycardia and/or hypotension associated with myocardial instability, which comprises a 5-HT_3 receptor antagonist, and a pharmaceutically acceptable carrier.

4. A method, use or composition according to any one of claims 1, 2 or 3, wherein the 5-HT_3 receptor antagonist is of formula (I), or a pharmaceutically acceptable salt thereof:

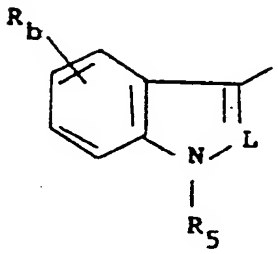
X-A-R (I)

wherein
X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;
A is a linking moiety; and
R is a saturated azabicyclic moiety or an imidazolyl moiety.

5. A method, use or composition according to claim 4 wherein X is of sub-formula (a), (b), (c), (d), (e), (f) or (g):



(a)



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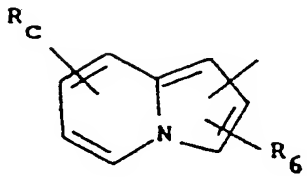
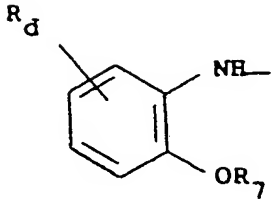
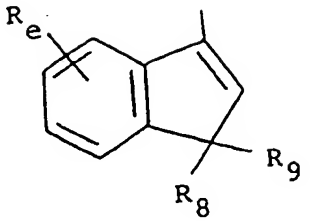


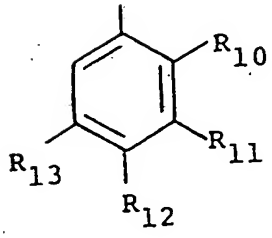
(c)



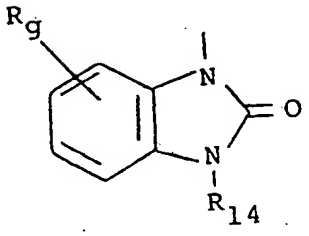
(d)



(e)



(f)



(g)

wherein

R_a to R_e and R_g are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene when R_1 is hydrogen;

R_8 and R_9 are independently selected from hydrogen or C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and

R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or

R_{10} and R_{11} are joined to form $-OCH(R_uR_v)-E-$ wherein E is $(CH_2)_n$ or $NR_wCO(CH_2)m$ wherein n is 1 or 2 and m is 0 or 1 and R_u, R_v and R_w are independently selected from hydrogen or C_{1-6} alkyl;

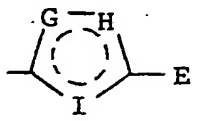
R_{12} is hydrogen, C_{1-6} alkoxy or amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl; and

L is CH or N.

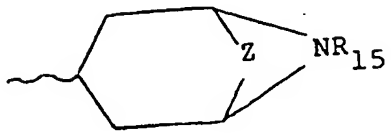
6. A method, use or composition according to claim 4 or 5 wherein A is CONH(amide), COO(ester), NHCONH (ureide), CONHCONH (extended ureide), or a group of structure (h):



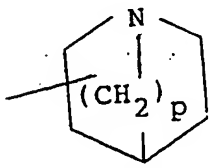
(h)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy.

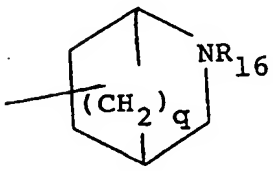
7. A method, use or composition according to claim 6 wherein R is of sub-formula (i), (j) or (k):



(i)



(j)



(k)

wherein

Z is $(CH_2)_n$ wherein n is 2 or 3, or Z is CH_2-O-CH_2;

p and q are independently 1 to 3; and

R_{15} or R_{16} is methyl or ethyl, preferably methyl.

8. A method, use or composition according to claim 7 wherein R is endo-9-azabicyclo[3.2.1]non-3-yl, endo-8-azabicyclo[3.2.1]oct-3-yl, 9-aza-3-oxabicyclo-[3.2.1]non-7-yl or 3-quinuclidinyl.

9. A method, use or composition according to claim 8 wherein the compound of formlula (I) is MDL 72222, ICS 205-930, granisetron or PU 46470A.

10. A method, use or composition according to claim 4 or 5 wherein A is $-CO-(CH_2)_2-$ and R is an imidazolyl moiety.

11. A method, use or composition according to claim 10 wherein R is 5-methyl-4-imidazolyl.

12. A method, use or composition according to claim 11 wherein the compound of formula (I) is ondansetron.

13. A method, use or composition according to claim 1, wherein the 5-HT_3 receptor antagonist is as described herein with reference to the listed patent publications relating to 5-HT_3 receptor antagonists.